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The spreading of radiolabelled fatty suppository bases in the human rectum

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Summary

The purpose of this study was to develop a radiolabelling method for assessing the spreading of fatty suppository bases (Witepsol H-5, W-35 and S-55), and to apply this technique to the evaluation of suppository disposition in the human rectum. ^{99m}Tc was bound chemically to the bases Witepsol H-5 and W-35, and mixed physically with Witepsol S-55. The spreading of each suppository base was monitored by gamma-scintigraphy following rectal administration. The mean radioactivity remaining at the inserted region 4 h after administration was 44.2% of total activity. The mean perpendicular maximum spreading distance from this region was 7.7 cm on the scintigram near to the sigmoid colon. Defecation was suggested to be a factor influencing the spread of suppository bases. However, there was no clear relationship between the type of suppository base used and the extent of its spread within the rectum.

Introduction

Recently, increasing attention has been paid to the intrarectal route as a means of systemic dosing and for the delivery of topically active drugs to the large intestine. Particularly, when a drug showing a significant first-pass effect is administered for a systemic purpose, the bioavailability is known to be dependent upon the site of absorption within the rectum. This can usually be explained in terms of the venous blood drainage within the rectum; the blood in the lower rectal area drains directly into the general circulation, whereas blood in the upper and middle rectal areas drains directly into the portal system and undergoes first-pass hepatic metabolism. It has been shown that when rectal doses of nitroglycerin (Kamiya et al., 1982) or lidocaine (De Leede et al., 1983) were allowed to spread upward from the anus to the upper rectum and lower intestine in rats, the bioavailability progressively decreased and approached oral bioavailability values.

In general, drug absorption rate from suppository is affected by several factors, solubility in water and suppository base, drug particle size and

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partition between the base and rectal fluid and so on. Particularly, when a drug is released slowly from suppository base and the release rate is the rate determining step for the bioavailability, the spreading of the molten base will affect the absorption rate of the drug and its absorption site.

Witepsol H-15 suppositories labelled with technetium hydroxymethyldiphosphonate (^{99m}Tc-HDP) have been used to obtain serial images by scintigraphy technique for evaluating the disposition of rectal dosage forms (Jay et al., 1985). Both enema and suppository were radiolabelled using anion exchange resin adsorbed with ^{99m}Tc-pertechnetate, have also been studied on the spreading after rectal administration in humans (Hay et al., 1982). However, these radiolabelling methods for assessing the spreading of rectal dosage forms do not seem to have been satisfactory from the viewpoint of uniformity of the radiolabelling in the suppository bases and retention of radioactivity in the suppository bases after rectal administration. The present study was therefore performed to develop a uniform radiolabelling method for suppositories (Witepsol H-5, W-35 and S-55), and to apply this technique to the evaluation of drug disposition in the human rectum.

Materials and Methods

Materials

Witepsol H-5 (lot. No. 056), W-35 (lot. No. 257) and S-55 (lot. No. 215) were supplied by Mitsuba Trading Co. (Tokyo, Japan). ^{99m}Tc was obtained as sodium pertechnetate solution by elution of a generator by Nihon Mediphysics Co. (Hyogo, Japan). Stannous chloride was obtained from Wako Pure Chemicals Co. (Osaka, Japan). Other reagents used were of analytical grade.

Preparation of radiolabelled suppository

Witepsol H-5 and W-35 were labelled chemically with ^{99m}Tc in the presence of a catalyst. Each suppository base (6.0 g) was melted at 40–45 °C, and mixed well with 0.4% $SnCl_2$ acetate buffer solution (0.5 ml, pH 2.0) as a catalyst and ^{99m}Tc-pertechnetate (6 mCi, 200 μl) for 5 min. The mixture was washed twice with 50 ml of warm water (40–50 °C) to remove unbound substances. It was then poured into a plastic suppository mold and allowed to cool. Witepsol S-55 was directly mixed with ^{99m}Tc-pertechnetate without any catalyst. Each suppository (2 g) contained a mean level of 600 μCi ^{99m}Tc.

Subjects

The preparations were rectally administered to 5 male volunteers, aged 26–41 years, weight 58–75 kg, height 169–170 cm. The subjects were healthy and none was taking medication of any kind.

Methods

All subjects ate a normal lunch 1 h before administration, and did not take any food or drink during the study. After administration of a suppository, each subject lay supine on a couch and remained in this position for 4 h. Sealed polyethylene tubes (0.5 × 0.2 cm o.d.) containing ^{99m}Tc were placed as anatomical reference markers at both iliac crests and the navel. In order to make the rectum anatomically clear, a lower GI X-ray radiograph was also obtained for each subject. Imaging was carried out using a gamma camera having a 37-cm-diameter field of view fitted with a medium-energy (300 keV maximum) parallel-hole collimator, and recorded data were fed in to a computer (Scintipac 2400, Shimadzu, Japan). The 140-keV photon emission of ^{99m}Tc was detected using a 30% energy window. Posterior and lateral views of the abdomen were recorded over a 4-h period at 30- and/or 60-min intervals, respectively. For analysis of the spreading behavior of the suppository in the rectum, the places where the radioactivity was found on the scintigrams were enclosed with frames (2 × 2 cm), and the ratio of the activity within each frame to the total activity was calculated (Fig. 1).

Results

Labelling of radionuclide in suppository bases

The radionuclide, ^{99m}Tc-pertechnetate, was ascertained to be completely bound to the molten

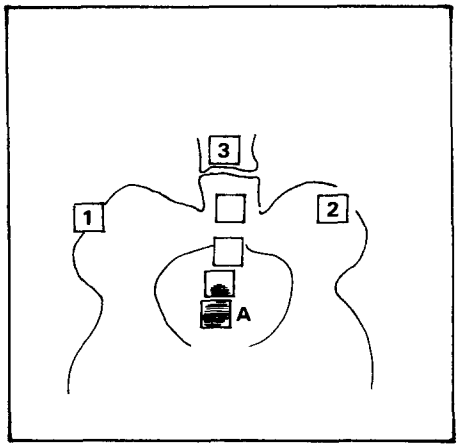

Fig. 1. Distribution of a suppository base (Witepsol H-5) 4 h after intrarectal administration to subject no. 2. A, place of insertion of suppository; 1, 2, iliac crests as extra markers; 3, navel as extra marker. Other frames are places where radioactivity was detected.

fatty suppository bases, Witepsol H-5 and W-35, and not be released into the water phase at all. The radionuclide distribution was also confirmed to be uniform when a sample of molten base was placed on the surface of water at 37–40 °C. The activity was trapped completely and uniformly in the fatty base and was not released into the aqueous phase after the radionuclide was physically mixed into Witepsol S-55, probably because the base contains surface-active agents and the radionuclide was trapped into the micelle. The melting points for the 3 bases after radionuclide labelling did not show any significant change.

Spreading of suppository

Fig. 1 shows a posterior scintigram of a Witepsol H-5 suppository at 4 h after rectal administration to subject no. 2. Region A was the area of

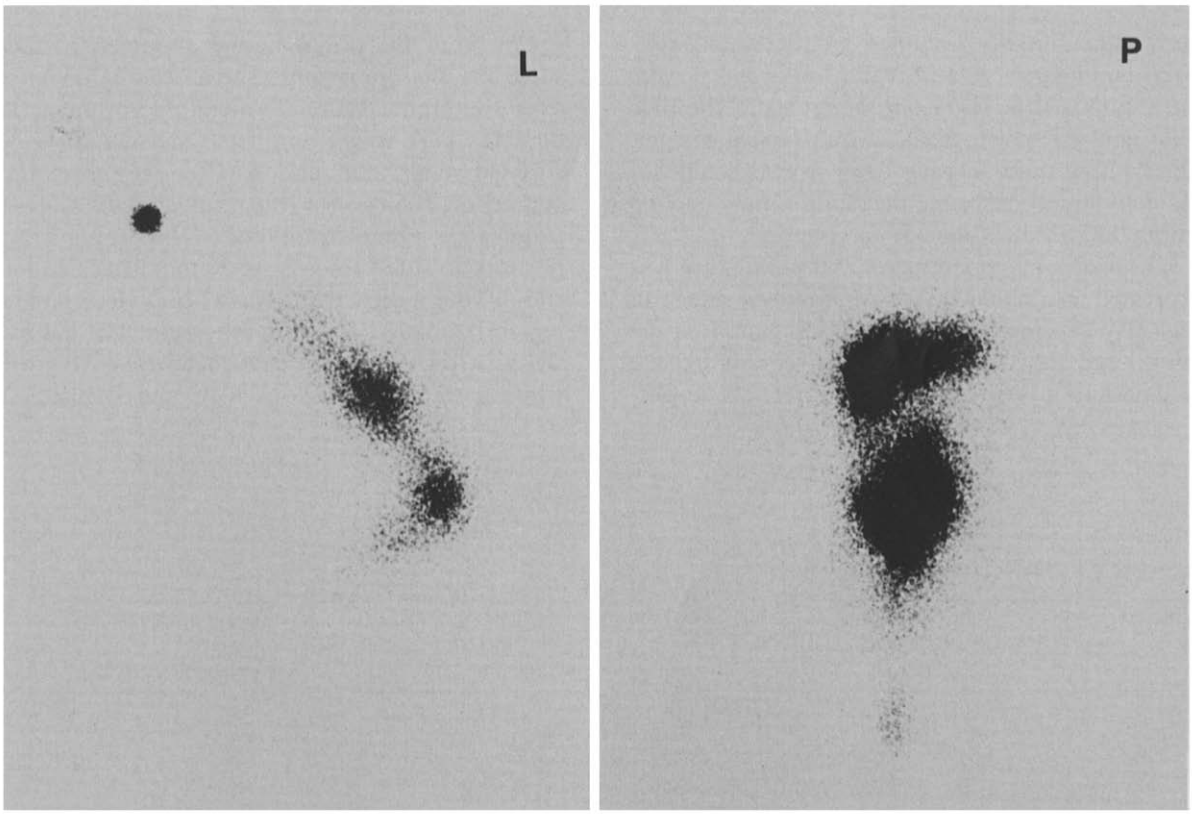

Fig. 2. Scintigrams of radiolabelled suppository (Witepsol H-5) in one of the subjects. L, lateral view at 150 min; P, posteriol view at 240 min.

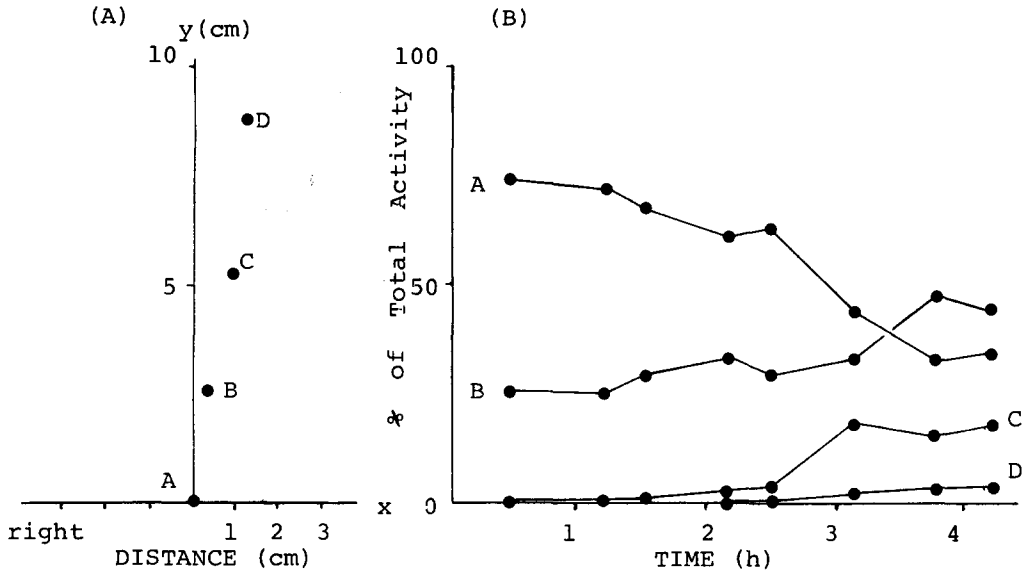

Fig. 3. Spreading of the suppository in the rectum in subject no. 2. A: plane and perpendicular coordinates are based on the scintigram shown in Fig. 1. B: Radioactivity–time curve during 4 h.

the rectum initially occupied by the suppository after administration, and regions 1, 2 and 3 were the anatomical markers on both sides of the iliac crest and the navel. Fig. 2 shows typical images. The melting time on each base in vivo could not be determined because the suppository melted within 30 min after the administration.

The extent of spreading on each scintigram was expressed as a rectangular coordinate as shown in Fig. 3A. The inserted position was placed at the origin, and the x-axis and y-axis represented the distances in a lateral and upper direction, respectively, from the origin in the abdomen as measured on the scintigrams. The spreading distances expressed in the figure are therefore not the actual ones for base migration, since the rectum is not situated along the mesion. Fig. 3B shows time course of changes in the radioactivity in each frame after administration of a Witepsol H-5 suppository to subject no. 2. At 30 min after administration, the radioactivity was already detectable in region B, about 2 cm from the origin. The radioactivity in region A gradually decreased with time while the levels in regions B, C and D increased

TABLE 1

Spreading of suppository bases in human volunteers

Subject no.	Time between defecation and dosing (h)	Suppository base	Remaining activity at the inserted region after 4 h	Maximum spreading distance (perpendicular) (cm)
1	22.0	Witepsol H-5	40.3 (%)	6.8
2	4.5	H-5	44.0	9.0
3	18.5	W-35	40.5	5.0
4	7.8	S-55	42.2	6.0
5	0	S-55	53.8	11.5
Mean ± S.D.	10.6 ± 9.35		44.2 ± 5.6	7.7 ± 2.6

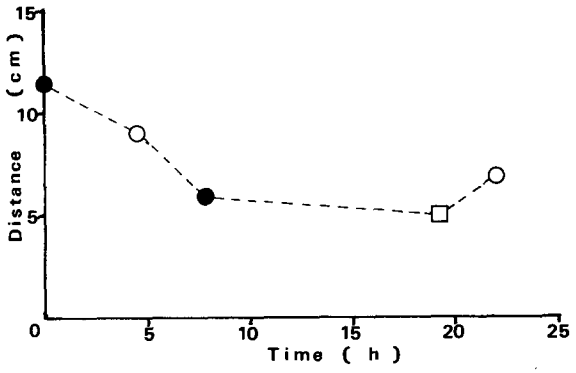

Fig. 4. Relationship between the spreading distance of suppositories and the time interval between defecation and dosing. Witepsol H-5 (○); Witepsol W-35 (□); Witepsol S-55 (●).

inversely. Part of the suppository base migrated to the upper part of the rectum (region D), 9 cm from the origin, within 4 h after administration. The radioactivity remaining at region A at 4 h was 44% of the total activity.

Table 1 shows a summary of the results for the 5 subjects. At 4 h after administration, 40–54% (mean 44.2%, $n = 5$) of the total activity remained at the inserted region. The range of the spreading distance in a perpendicular direction was 5.0–11.5 cm (mean 7.7 cm, $n = 5$) on the scintigrams. However, none of the subjects showed detectable radioactivity in the sigmoid colon at 4 h after administration.

Relationship between spreading of suppository and defecation

The spreading distance seemed to be inversely correlated with the time of defecation before dosing. All of the subjects who participated were regular in their bowel habits. The greatest spreading occurred in subject no. 5 who was dosed immediately after defecation. Subject no. 3, in whom the least spreading occurred, had defecated 18.5 h before dosing. Up to a time interval of 7 h after defecation, the spreading of the suppository base was reduced as the time interval between dosing and defecation increased, then reached a plateau value, irrespective of the type of suppository base used, as shown in Fig. 4.

Discussion

The purpose of this study was to develop a new radiolabelling method for assessing the spreading of fatty suppository bases, and to obtain information on the disposition of drugs in the human rectum. For the labelling of rectal dosage forms, i.e., enema solutions (Hay et al., 1982; Wood et al., 1985), foams (Hay et al., 1979; Wood et al., 1985) and suppositories (Hay et al., 1982), physical mixing with an anion exchange resin onto which ^{99m}Tc-pertechnetate has been adsorbed has been frequently used with semi-solid or solution dosage forms. Although the resin tends to be localized in the lower part of the suppository base after melting, we have found that its distribution in the base is generally irregular. ^{99m}Tc-HDP has previously been mixed directly with a suppository base (Jay et al., 1985). This approach, however, may give somewhat erroneous values of spread because radionuclide has been observed to be released rapidly from the fatty base into the aqueous phase after melting in our in vitro studies.

In our simple method reported here, the radionuclide pertechnetate was completely bound to the suppository bases, and showed a uniform distribution. The melting points of the bases used did not change after radionuclide labelling. The spreading of suppositories was limited to the rectal region, and did not reach the sigmoid colon. This result agreed with those obtained in other studies (Hay et al., 1982; Jay et al., 1985; Wood et al., 1985). In addition, we found that half of the suppository remained at the inserted position even at 4 h after administration, suggesting that a drug may be absorbed mainly at the lower part of the rectum if it is released rapidly from the base. In this study, defecation was suggested to be a factor influencing the spreading of the base. The rectum contents may interfere with the spread of a suppository base. Wood et al. (1985) suggested that the antegrade movement of the colon contents inhibited the spreading of rectal dosage forms, both enema solutions and foams.

In conclusion, the radiolabelling method reported here was useful for assessing the spreading of fatty base suppositories. The pharmacokinetic data obtained should add to that already known

on the relation between drug absorption and the spread of a suppository base.

Acknowledgements

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